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Engagement of mechanisms of cellular differentiation in formation of memory traces

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The article concerns study of the effect of antibody-mediated blockade of serotonin-modulating anticonsolidation protein (SMAP), being in linear relation with serotonin, on the formation of memory in the rats on the conditioned models of alternative running and 2-lever operant differentiation with food reinforcement, as well as on the level of nerve growth factor (NGF) in the brain structures. In the 1st series of studies in the rats, achieved 80% level of correct trials on the model of alternative running, through ELISA-test the level of SMAP was evaluated in the brain occipital and temporal cortex. Significant downregulation ($p<0.001$) of SMAP in the temporal cortex of the trained rats was noticed. In the 2nd and 3rd series of studies a single intra-cerebral administration of the anti-SMAP antibodies prior to learning sessions brought to much quicker ($p<0.001$) formation of the memory (50% level of correct trials), than in the intact and control (non-immune γ-globulins) animals, as well as to a significantly quicker decrease of latency of the first running towards the platform or lever ($p<0.01$). In the 4th series of studies 24 h later since intra-cerebral administration of anti-SMAP antibodies induced downregulation of NGF in the hippocampus ($p<0.001$) and left parietal cortex ($p<0.001$), whereas 3 days later downregulation of NGF in the left parietal cortex ($p<0.001$) and its upregulation in the hippocampus ($p<0.001$) were noticed. It is proposed that, promoting effects of antibodies-mediated blockade of SMAP on the formation of memory traces are related to its negative regulation of cellular differentiation.

Keywords: *Serotonin-modulating anticonsolidation protein, antibodies, memory, indirect ELISA-test, nerve growth factor, hippocampus, left parietal cortex*

INTRODUCTION

In spite of long-term history of studies of the role for serotonin in the processes of memory, up to now still there is no complete clearness of understanding concerning character of its engagement in these processes, as besides tremendous amount of publications showing promoting effects of serotonin on memory formation (Harvey, 1995; Barrionuevo et al., 2000; Cassel, 2010), there are literature data as well about blocking effects of abundant level of serotonin on these processes (Essman, 1974; Getsova et al., 1980; Vanderwolf, 1989; Santucci et al., 1996). Furthermore, of not less importance is exploration of the mechanism of participation of serotonin in the process of memory consolidation.

Presently the widely accepted is a statement saying that in the basis of memory formation lies advent of novel synaptic connections between neurons involved into the process of remembering. In experimental way this standpoint is supported by the results of ultra-structural investigations revealing increase of a number of dendritic spines in the brain cortex of the trained animals or animals kept under informational-enriched conditions (Leuner, Shorts, 2004).

The studies undertaken by different researchers last years, demonstrate engagement of newly-formed neurons in the brain structures of

the mature organisms (neoneurogenesis) in the formation of memory traces (Sherstnev et al., 2010; Sherstnev et al., 2015).

Earlier conducted studies showed that intracerebral administration of serotonin-modulating anticonsolidation protein (SMAP), identified in the brain cortex and purified from the whole brains of the rats and being in linear relations with serotonin (Mekhtiev, 2000), impairs processes of memory consolidation in the conditioned models with negative and positive reinforcement (Guseinov, Mekhtiev, 2013; Mekhtiev et al., 2015). Besides, formation of these tasks in the rats till reaching 80% of correct trials leads to pronounced downregulation of SMAP in the brain cortex (Mekhtiev et al., 2015).

Proceeding from the mentioned above data, the attempt of clarification of input of molecular mechanisms underlying differentiation of the precursors of nervous cells, into the formation of traces of long-term memory was undertaken. For the purpose of solving of this problem the effects of antibodies-mediated blockade of SMAP activity on the formation of memory traces in the conditioned models of alternative running and 2-lever operant differentiation with food reinforcement as well as on the levels of nerve growth factor (NGF) in the hippocampus and left and right parietal areas of the brain cortex were analyzed.

MATERIALS AND METHODS

Biochemical methods. SMAP was purified from the cow brains. The brains were homogenized in the extracting buffer containing 0.05 M phosphate buffer (pH 7.2), 0.3 M NaCl, 5 mM EDTA and 0.1% Triton X-100 in a volume ratio of tissue and buffer as 1:4. The main stages of fractionations were as follows: 1) partial precipitation by ammonium sulfate under the final concentration 40%, 2) gel-chromatography on the column (3 X 60 cm) of Sephadex G-150. The process of fractionation and selection of the immunopositive fractions was realized under the control of indirect ELISA-test with application of anti-SMAP polyclonal immunoglobulins (Mekhtiev, 2000).

Anti-SMAP polyclonal immunoglobulins were produced through 5-6-month immunization of the male rabbits of Chincilla species by subcutaneous administration of 300 μg of the purified correspondent protein per animal, in a mixture with complete Freund adjuvant (Sigma, Germany).

Measurements of the levels of SMAP and NGF in the brain cortex and hippocampus were carried out by indirect ELISA-test (Antibodies Volume II: Practical Approach) on the polystyrene plates with moderate level of adsorption (Sigma, Germany) with application of rabbit polyclonal immunoglobulins to SMAP and NGF (2.5 S; Sigma Immunochemicals, Germany). Owing to involvement of brain cortex in the formation and storage of memory traces, during realization of the ELISA-test total proteins of the occipital cortex (processing and storage of visual information) and parietal (participation in associative learning) cortex of the brain were used. The animals had been anesthetized and sacrificed, and the hippocampus and left and right areas of parietal cortex were removed and frozen under a temperature of -70°C. Prior to the beginning ELISA-test, the water-soluble proteins were extracted from the studied samples. Those proteins were extracted in the extraction buffer (pH 7.3) and their concentrations were brought up to 20 μg/mL with 0.1 M Tris-HCl buffer (pH 8.6). Each sample was repeated three times and on finalization of the reaction the average values of three samples were calculated. The concentrations of the total proteins were measured on Bredford technique with application of 0.01% solution of Coumassi G-250 on the wavelength 595 nm. Immunoglobulins to SMAP and NGF (2.5 S; Sigma Immunochemicals, Germany) were used as the first antibodies, while goat anti-rabbit immuneglobulins with conjugated horseradish peroxidase (Sigma Immunochemicals, Germany) were used as the second antibodies. Visualization of the reaction was realized with application of substrate of horseradish peroxidase – 0.05% orthophenilendiamine in 0.05 M citrate-phosphate buffer (pH 4.5). The reaction was stopped 30 min later from addition of substrate by addition of 3 M solution of NaOH. The results of the reaction were digitalized in the photometer for the ELISA-test “Spectra Max 250” (Molecular Devices Co., USA) on the wavelength 492 nm.

Anti-SMAP polyclonal antibodies were purified from the solution of anti-SMAP immunoglo-

bulins through a technique of immune-affinity chromatography performed on the column (0.5 X 3 cm) of CNBr-Sepharose (Sigma, Germany) with covalently immobilized SMAP (Mekhtiev, Asadova, 2018). After application of anti-SMAP immunoglobulins onto the column, it was thoroughly washed with 20 column volumes of 0.01 M phosphate buffer (pH 7.2) and under the extinction control (method by Bradford) specifically bound anti-SMAP antibodies were eluted by chaotropic agent 3 M KCNS. The eluted antibodies were dialyzed against 0.15 M NaCl, buffered up to the value of pH 7.2, and frozen. In a single cycle, up to 12 mg antibodies were eluted from the affinity column.

Physiological methods. In the 1st series of studies the behavioral experiments were carried out on the 5-6-month-old Wistar male rats on the difficult for acquisition conditioned model of alternative running with food reinforcement (Semyonova, 1976). The experimental box was made from organic glass with dimensions 60 X 60 cm. The platforms of sizes 20 X 10 cm were secured to the left and right corners of the box, at the height of 16 cm from the bottom of the box. The animals were culled into 2 groups: 1) control group (n=13); 2) experimental group (n=12). The animals of the experimental group were put onto the start platform at the entrance of the experimental box and their running and climbing onto the left and right platforms were reinforced by food pellets of mass 200 mg, placed on them and composed of sunflower oil, millet flour, ground corn grains and combined fodder. After animal's running towards the platform and eating the fodder on one side, it was placed again onto the starting platform and its running to the opposite side was reinforced. The pellets were placed onto the platforms at the time, when animal could not see it.

The learning sessions lasted for 7 days, daily, 20 trials each day. The trial was considered as correct, if after returning to the starting platform the next trial was done towards opposite side. Criterion of successful learning was calculated on ratio of a number of correct trials to a total amount of trials during single learning session. The learning was lasted up to reaching 80% of correct trials, the animals were sacrificed, the occipital and parietal areas of the brain cortex were removed and frozen. The animals of the control group as well as the animals of the experimental group were deprived of food and put into the experimental box without learning for a timeframe correspondent to the timeframe of the experimental animals.

In the 2nd series the studies were also carried out on the model of alternative running. In this series of studies the rats were culled into 3 groups: (1) intact group (n=13); (2) control group – rabbit non-immune γ-globulins (n=13); (3) experimental group – rabbit anti-SMAP antibodies (n=12). The animals were anesthetized with natrium etaminali (40 mg per 1 kg of body mass) and administered with 10 μl of preparations at a concentration of 1.5 mg/ml in the saline buffered to pH value of 7.2 into the brain left lateral ventricle. The learning sessions were undertaken 24 h after administration of the preparations till reaching by the animals of 50% criterion of correct trials. In this case, the latencies of the first trials towards the platform and ratio of correct trials to total amount of trials in percent were measured. The animals of the control group as the animals of the experimental group were deprived for food and placed into the experimental box for the time similar to the time of the animals of the experimental group.

In the 3rd series the studies were carried out on the model of 2-level operant differentiation model. The rats were culled into 3 groups: 1) intact group (n=13), 2) control group – rabbit non-immune γ-globulins (n=13) and 3) experimental group – anti-SMAP antibodies (n=12). During the learning sessions the animals were trained to press the right lever of the two levers secured to the back wall of the experimental box close to each other to get food pellet as reinforcement. The animals in this series of studies were administered the preparations the same way and the time interval between injections and beginning of learning sessions were the same as in the 2nd series of studies.

In the 4th series of studies the effect of administration of anti-SMAP antibodies into the brain left lateral ventricle on the levels of NGF in the hippocampus, right and left parietal cortex of the rats was analyzed. The rats were culled into 3 groups: 1) intact group (n=7), 2) control group – rabbit non-immune γ-globulins (n=8) and 3) experimental group – anti-SMAP antibodies (n=7). The animals in this series of studies were administered the preparations the same way and the time inter-

vals between injections and onset of learning sessions were the same as in the 2nd and 3rd series of studies. 24 h or 3 days later the rats were sacrificed, hippocampus, right and left parietal cortex were removed from the brain, water-soluble proteins were extracted and used as antigens in the indirect ELISA-test whose stages are detailed above.

The results of the 2nd, 3rd and 4th series of studies were grouped and analyzed by Student's t-criterion.

RESULTS

In the 1st series of studies after animals' reaching 80% criterion of correct trials in the model of alternative running the following regularities were revealed. In the course of elaboration of the task permanent increase of correct turn-by-turn trials to left and right platforms, climbing onto them and consuming food pellets were observed. In this case in the 1st day of learning sessions in the first 1-2 min later from putting the animals into the box, they stayed mostly in one of the corners demonstrating the mere signs of anxiety in the form of uninterrupted trembling and freezing. 2-3 min later they started to thorough exploration and sniffing of the box, looking for food and in different timeframes the animals climbed onto one of the platforms and consumed the food pellet. On the 2nd day after putting into the box the animals on the first minute again demonstrated the signs of anxiety, but thereafter they quickly passed to thorough exploration of the box. Beginning from the 4th experimental day the animals very quickly entered the box, without delay came up to the platforms and climbed onto them.

In the 1st series of studies evaluation of SMAP levels in the occipital and parietal cortex of the brain revealed significant downregulation (by 25.3%) of SMAP in the parietal cortex of the animals of the experimental group, reached 80% criterion of correct trials on the alternative running model relatively to the rats of the control group ($p<0.001$ on Student's t-criterion; Fig.1). In the occipital cortex no changes of SMAP level in the trained animals in comparison to the control values were noticed (Fig. 1).

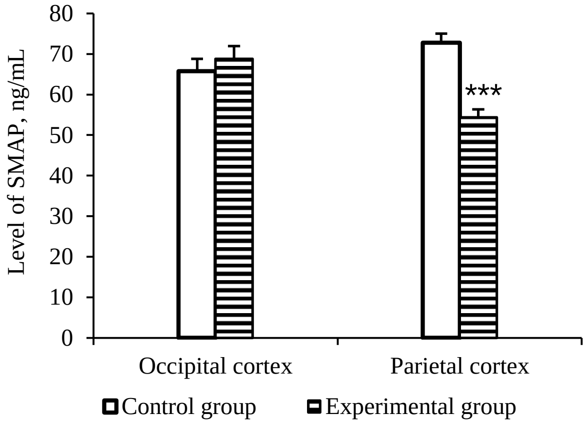


Fig. 1. The levels of SMAP in the occipital and parietal cortex of the rats, reached 80% criterion of correct trials in the alternative running model.
*** - $p<0.001$.

In the 2nd series of studies administration of anti-SMAP antibodies into the brain lateral ventricle of the rats 24 h prior to learning sessions in the conditioned model of alternative running significantly facilitated elaboration of the task. In particular, if the animals of the intact and control groups reached 50% learning criterion on the 7th experimental day, then under the effect of anti-SMAP antibodies the animals of the experimental group reached this criterion on the 4th day ($p<0.001$ on Student's t-criterion; Fig. 2).

Furthermore, though the dynamics of downregulation of the latencies of the first trial towards the platform was observed in the all studied groups, nevertheless in the experimental group this downregulation bore steeper character ($p<0.01$; Student's t-criterion; Fig. 3). So, the obtained data indicate to stimulating effect of anti-SMAP antibodies on memory formation and, correspondently, to negative character of regulation of this process by SMAP.

In the 3rd series of studies administration of anti-SMAP antibodies into the brain lateral ventricle of the rats 24 h prior to learning sessions in the complicated and time-consuming conditioned 2-lever operant differentiation model significantly promoted and strengthened the formation of memory.

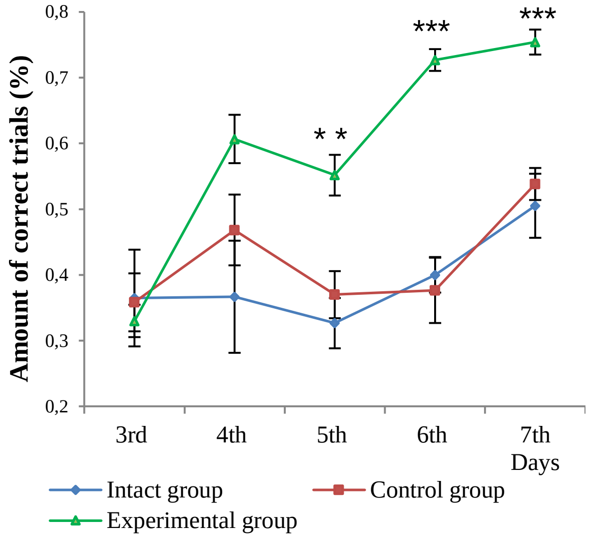


Fig. 2. Effects of anti-SMAP antibodies on the dynamics of memory formation in the alternative running model. ** - p<0.01; *** - p<0.001.

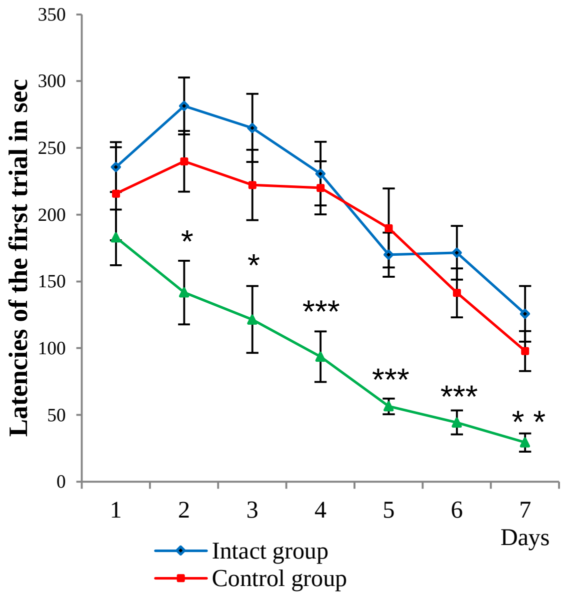


Fig. 3. Effects of anti-SMAP antibodies on the latencies of the first trial in the alternative running model. * - p<0.05; ** - p<0.01; *** - p<0.001.

If the animals of the intact group reached 50% criterion of correct trials on the 7th experimental day and the control animals reached this criterion on the 6th day, then the animals of the experimental group reached the level of 50% correct trials on 4th day (p<0.001; Student's t-criterion; Fig. 4). Besides of a hallmark of the rate of achieving 50% learning criterion, each group had its upper limit of correct trials (plateau), no matter how long the learning sessions lasted. So, the plateau for the animals of the intact group made 50%, the plateau for the control rats – 55%, and the plateau for experimental group – 80% (Fig. 4).

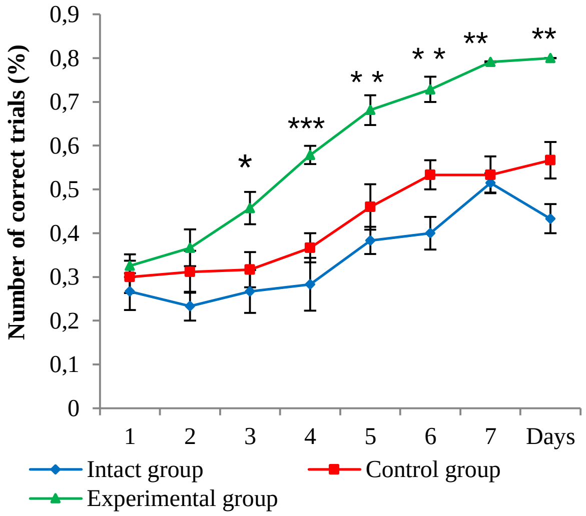


Fig. 4. Effects of anti-SMAP antibodies on the dynamics of memory formation in the model of 2-lever operant differentiation. * - p<0.05; ** - p<0.01; *** - p<0.001.

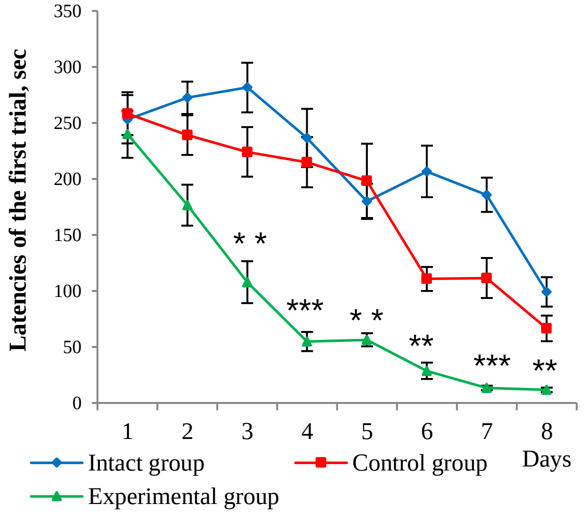


Fig. 5. Effects of anti-SMAP antibodies on the latencies of the first trial in the model of 2-lever operant differentiation. **- p<0.01; *** - p<0.001.

As in the 4th series, the dynamics of downregulation of the latencies of the first trial towards the lever was observed in the all studied groups, however, in the experimental group this downergulation had much steeper character ($p<0.01$; Student's t-criterion; Fig. 5).

In the 4th series of studies the effect of intra-cerebral administration of anti-SMAP antibodies on the levels of NGF in the hippocampus, brain right and left parietal cortex was evaluated. It was shown that 24 h later since intra-cerebral administration of anti-SMAP antibodies, downregulation of NGF in the hippocampus ($p<0.001$ on Student's t-criterion; Fig. 6) and left parietal cortex ($p<0.001$ on Student's t-criterion; Fig. 6) was revealed, whereas in the right parietal cortex the level of NGF did not change.

At the same time, 3 days later from intra-cerebral administration of anti-SMAP antibodies downregulation of NGF in the left parietal cortex having still been maintained ($p<0.001$ on Student's t-criterion; Fig. 7), although in the hippocampus its significant upregulation was revealed ($p<0.001$ on Student's t-criterion; Fig. 7).

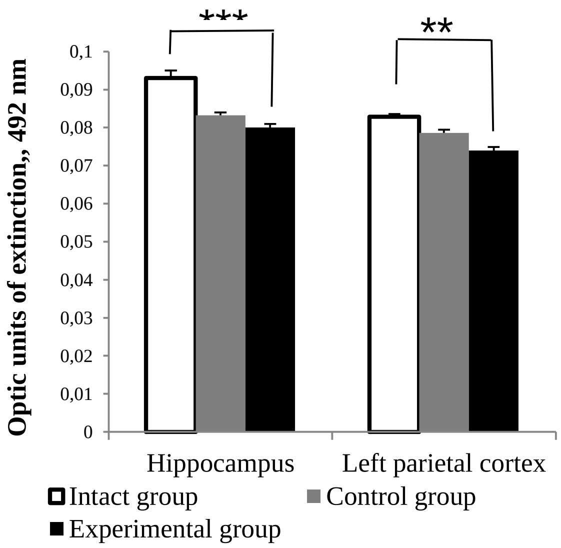


Fig. 6. Effects of anti-SMAP antibodies on the level of NGF in the hippocampus and left parietal cortex 24 h after antibodies administration. *** - $p<0.001$.

So, the obtained results in these series of studies indicate to downregulation of SMAP in the parietal cortex of the brain through elaboration of the conditioned alternative running model. Besides, the results indicate to accelerating and strengthening the formation of memory traces in the rats on the complicated conditioned models under antibodies-mediated blockade of SMAP. Moreover, 24 h later after intra-cerebral administration of SMAP downregulation of NGF in the hippocampus and left parietal cortex of the rat brain, though 3 days after their administration downregulation of NGF was noticed in the left parietal cortex, while in the hippocampus its upregulation was revealed.

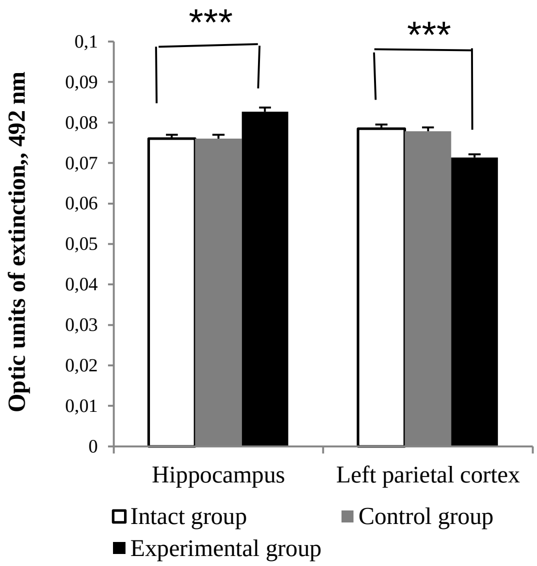


Fig. 7. Effects of anti-SMAP antibodies on the level of NGF in the hippocampus and left parietal cortex 3 days after antibodies administration. *** - $p<0.001$.

DISCUSSION

While considering downregulation of SMAP in the brain cortex of the trained animals in the many-time conditioned model of alternative running with food reinforcement and in the earlier undertaken studies on the shuttle box model with electroshock reinforcement (Guseinov, Mekhtiev, 2013) as well as promoting effect of anti-SMAP antibodies on the formation of memory traces on the model of alternative running and 2-lever operant differentiation, one can come to a reasonable conclusion about existence of SMAP-mediated negative regulation of the formation of memory traces. The revealed promoting effects of anti-SMAP antibodies on the formation of memory coincide with the earlier obtained data on the bloc-

king effects of intra-cerebral administration of SMAP itself on elaboration of the task in the shuttle box model (Guseinov, Mekhtiev, 2013) and in the model of alternative running (Mekhtiev et al., 2015).

The studies conducted by different researchers revealed that formation of memory traces induces the formation of novel cellular elements in the brain structures of the mature organisms (neoneurogenesis; Sherstnev et al., 2010; Deng et al., 2010; Sherstnev et al., 2015; Yau & So, 2015). Furthermore, the newly-formed neurons should pass through the stages of differentiation and specialization and, finally, be integrated into the functioning of the brain structures, that have already been formed in ontogenesis. For this purpose these neurons should sprout their axons and form new synaptic connections with other neurons, i.e. they should become a part of new neuronal circuits.

In the embryonic period of development of the organism, neurogenesis in the brain cortex is realized through migration of neuroblasts, formed in generative ventricular zone, i.e. in the zone of hippocamp, towards cortical plate along certain glial cells, called “radial glia” and realizing the role of the cellular conductors (Nadarajah et al., 2003). Radial glia realizes this function by “directional” molecules, in particular molecules of cellular adhesion, obviously, lined along the designed migration route of neuroblasts. The neuronal precursors are formed in the hippocampus also in postnatal ontogenesis (neoneurogenesis), however, in the mature organisms they migrate towards the cortex through another mechanism. In this case the neuronal precursors within the rostral migratory stream migrate first into bulbus olfactorius, where they are directed further to the points of their final localization (Sawada et al., 2011; Kaneko et al., 2017). Interestingly, the phenotypic peculiarities of the differentiated newly-formed neurons are generated in their cellular precursors before the beginning of migration and do not change after its finalization and arrival of the cells to the point of destination (Merkle et al., 2007). Hence, under the effect of molecular signals, released from the microenvironment of precursor cells in the course of migration and in the point of their arrival, their phenotypic profiles do not change. In the light of processes of formation of long-term memory this fact, probably, means that the neuronal precursors, modified under the effect of elaborated task in the hippocampus, are capable to maintain differentiated changes till the end of migration.

Presently it is revealed that ablation of the bulbus olfactorius in the animals brings to noticeable changes in their behavior, including impairment of memory storage, worsening with time course passed since the operation (Yamamoto et al., 1994; Yamamoto, Watanabe, 1997). In this case, it was found that bulbectomized rats had morphological changes in the form of the atrophy of dendritic spines and significant decrease of the total length of dendrites in the hippocampus and piriform cortex as well as downregulation of cellular proliferation in the dentate gyrus of the hippocampus (Morales-Medina et al., 2013). Proceeding from the revealed rough impairment of memory storage in the animals through bulectomy and taking into account engagement of bulbus olfactorius in migratory processes, one can propose that these disturbances are as well related to the impairment of migration of newly-formed neurons in the mature animals.

The literature data demonstrate that downregulation of NGF in the brain structures of the mature organisms promotes strengthening of differentiation processes of the precursors of the nervous cells, though its upregulation reflects strengthening of proliferative activity of precursor cells (Liu et al., 2014). The significant downregulation of NGF in the hippocampus and left parietal cortex in the rats 24 h later since intra-cerebral administration of anti-SMAP antibodies, revealed in the 4th series of studies, apparently, reflects strengthening of the processses of differentiation of the precursors of the cellular elements. Furthermore, the observed 3 days later downregulation of NGF in the left parietal cortex is, perhaps, related to continuing mighty cell differentiation, though parallel upregulation of NGF in the hippocampus, perhaps, induces increased proliferative activity. Probably, the precursor cells, starting their differentiation 24 h later from administration of SMAP, migrate from the hippocampus into the brain cortex. Moreover, 3 days later from the administration of antibodies, in the hippocampus the processes of cellular differentiation are strengthened for the purpose of restoration of a part of the pool of the precursor cells lost due to their migration into the cortex.

Perhaps, the revealed stimulatory effect of the antibodies-mediated blockade of SMAP on the formation of memory traces in the complex conditioned models is directly related to its negative regulatory activity regarding to differentiation of cellular elements. Besides, earlier on the model of embryonic development of *Xenopus laevis* we demonstrated that addition of anti-SMAP antibodies to the incubation medium of the embryos accelerates noticeably their passing through the stage of metamorphosis (Aminov, Mekhtiev, 2017). Hence, on the basis of the results obtained in this study and earlier undertaken studies one can make a conclusion that in the course of consolidation of the obtained information in the brain structures of the mature organisms differentiation and functional specialization of the newly formed neurons occur, and these processes last continuously throughout the whole lives of the individuums.

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Yaddaş izlərinin yaranması prosesində hüceyrə differensiasiyası mexanizmlərinin iştirakı

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Məqalə qida möhkəmlənməsi ilə yaranan növbəli qaçış və instrumental differensiasiya şərti-reflektor modellərində erkək siçovullarda yaddaş yaranmasına, həmçinin beyin strukturlarında sinir böyümə faktoru (SBF) miqdarına serotonin ilə düz mütanasib əlaqədə olan serotonin-modullu antikonsolidasiya zülalının (SMAZ) anticisimlər vasitəsilə blokadasının təsirinin öyrənilməsinə həsr olunub. Tədqiqatların 1-ci seriyasında növbəli qaçış modelində düzgün cavabların 80% səviyyəsinə çatmış siçovulların beyin qabığının ənsə və təpə nahiyələrində SMAZ-ın miqdarı müəyyən edilib. Öyrənilmiş siçovulların beyin qabığının təpə nahiyəsində SMAZ-ın miqdarının ciddi dərəcədə azalması ($p<0.001$) müşahidə olunur. Tədqiqatların 2-ci və 3-cü seriyalarında təlim seanslarından əvvəl siçovullara SMAZ-a qarşı anticisimlərin beyindaxili birdəfəlik yeridilməsi kontrol (qeyri-immun γ-qlobulinlər) və intakt heyvanlara nisbətən onlarda vərdişlərin daha tez yaranmasına ((düzgün cavabların 50%-lı meyarı; $p<0.001$), habelə platformaya və ya qola doğru birinci qaçışın latent dövrünün daha tez azalmasına ($p<0.01$) gətirib çıxarır. Tədqiqatların 4-cü seriyasında siçovullara SMAZ-a qarşı anticisimlərin beyindaxili yeridilməsi 24 s sonra hippokampda ($p<0.001$) və baş beynin sol təpə nahiyəsində ($p<0.001$) SBF-nun miqdarının azalması ilə nəticələnir. Halbuki, 3 gün sonra SBF-nun miqdarının sol təpə qabığında azalması ($p<0.001$), hippokampda isə artması ($p<0.001$) müşahidə olunur. Güman edilir ki, SMAZ-ın anticisimlər ilə blokadasının yaddaş izlərinin yaranmasına stimuləedici təsiri onun hüceyrə elementlərinin differensiasiyasını neqativ tənzimləməsi ilə əlaqədardır.

Açar sözlər: *Serotonin-modullu antikonsolidasiya zülalı, anticisimlər, yaddaş, dolayı immuno-enzim analizi, sinir böyümə faktoru, hippokamp, sol təpə qabığı*

Участие механизмов клеточной дифференциации в процессе формирования следов памяти

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Статья посвящена изучению влияния блокады антителами активности серотонин-модулируемого антиконсолидационного белка (СМАБ), находящегося в прямой зависимости от уровня серотонина, на формирование памяти у крыс-самцов в условно-рефлекторных моделях чередования побежек и инструментального дифференирования с пищевым подкреплением, а также на уровень фактора роста нервов (ФРН) в структурах головного мозга. В 1-й серии исследований в затылочной и теменной областях коры головного мозга крыс, достигших 80% -го уровня правильных ответов, в модели чередования побежек методом иммуноферментного анализа определяли уровень СМАБ. Было обнаружено заметное снижение ($p<0.001$) уровня СМАБ в теменной области коры у обученных животных. Во 2-й и 3-й сериях исследований однократное внутримозговое введение антител к СМАБ крысам до сеансов обучения приводило к значительно более быстрому формированию у них навыков (50%-й критерий правильных ответов), чем у контрольных (неиммунные γ-глобулины) и интактных животных ($p<0.001$), а также к более быстрому снижению латентного периода первой побежки к платформе или к рычагу ($p<0.01$). В 4-й серии исследований внутримозговое введение крысам антител к СМАБ через 24 ч вызывало снижение уровня ФРН в гиппокампе ($p<0.001$) и левой теменной области ($p<0.001$) головного мозга, тогда как через 3 суток – снижение уровня ФРН в левой теменной коре ($p<0.001$) и повышение его уровня в гиппокампе ($p<0.001$). Возможно, что стимулирующее влияние блокады СМАБ антителами на формирование следов памяти обусловлено его негативной регуляцией дифференциации клеточных элементов.

Ключевые слова: *Серотонин-модулируемый антиконсолидационный белок, антитела, память, непрямой иммуноферментный анализ, фактор роста нервов, гиппокамп, левая теменная область коры головного мозга*